REMARKS

In the Office Action dated April 20, 2005, claims 15-31 were examined with the result that all claims were rejected. The Examiner made the rejection final. In response, Applicant has canceled claims 15-19 and 31, and rewritten claims 20-22 and 30. In view of the above amendments and following remarks, reconsideration of this application is requested.

On page 2 of the Office Action, the Examiner objected to the disclosure stating that although various trademarks have been capitalized, they appear not to be accompanied by the generic terminology for the marks. Accordingly, Applicant has revised the description and inserted generic terminology for each identified product. In some cases, the terms referred to by the Examiner were being utilized merely as company names, and in those locations, Applicant has corrected the description to indicate that the marks are not being utilized as trademarks for a product, but instead as the name of a company from which such products could be obtained. Applicant believes it has corrected all of the trademark descriptions noted by the Examiner on page 2 of the Office Action, and accordingly, requests the Examiner withdraw the objection to the description issued on this basis.

On page 3 of the Office Action, the Examiner rejected claims 1-3 and 5-13 under §112, first paragraph. However, Applicant believes this rejection must be in error as claims 1-3 and 5-13 were previously canceled. Thus, Applicant believes this rejection is moot.

At the bottom of page 3 of the Office Action, the Examiner rejected claims 15-18 under 35 USC §102(b) as being anticipated by Bush et al. In response, Applicant has canceled claims 15-18 via the present Amendment. Accordingly, Applicant believes this rejection is now moot.

At the top of page 6 of the Office Action, the Examiner objected to the brief description of the drawings as being improper. In response, Applicant has submitted a revision to the description which describes each Figure with a new sentence. Applicant

has proposed inserting these new descriptions at page 3 of the specification as filed, and then inserting a new heading entitled "Detailed Description of the Invention" and thereafter retaining the previous descriptions of the drawings. It appeared to Applicant that this would be a "cleaner" way of overcoming the Examiner's objection, rather than attempting to modify the paragraphs originally discussing the drawings. Obviously, by doing this, those original paragraphs become part of the "Detailed Description of the Invention" section of the application. Thus, Applicant requests approval of the current addition of the Description of the Drawings as none of this material would be considered new matter. In light of this modification to the Description, Applicant requests the Examiner withdraw the objection to the drawings.

On page 6 of the Office Action, the Examiner also rejected claim 30 under 35 USC §112, first paragraph as failing to comply with the written description requirement. The Examiner has objected to claim 30 stating that the claims are drawn to a genus of polypeptides that are not adequately defined in the specification as filed.

In response, however, Applicant notes that claim 30 is not claiming or drawn to a genus of polypeptides. Instead, the claim is drawn to a "method for the detection of a disorder" and now sets forth nine steps for detecting those disorders. The Examiner believes that polypeptides such as "prion protein fragments", "beta protein fragment" and the like are not accurately described. However, it is important to note that complete or partial structures of such fragments, physical and/or chemical properties, and methods of making these fragments are all well known to those skilled in the art and most importantly, their structures, properties, function and the like are not necessary to being able to perform the steps of the present invention as defined in claim 30. In other words, one of the steps of claim 30 is to contact proteons produced in a subsample with an antibody that binds to various listed proteins. It is not necessary to define the specific prion protein fragment, beta protein fragment, etc. because one skilled in the art would recognize that the step involves binding an antibody to such fragment, irregardless of the structure, properties, and/or functions of said fragments. Thus, Applicant is not claiming

a genus of polypeptides, but instead is claiming the step of contacting proteons in a subsample to an antibody that binds to any one of those polypeptides. Again, one skilled in the art would readily recognize that no matter what the structure, property or function of said fragments might be, it is the step of antibody binding to that fragment that is important to claim 30. Thus, Applicant believes claim 30 does adequately claim the invention in sufficient detail so that one skilled in the art would be able to practice the invention of claim 30.

At page 8 of the Office Action, claims 30-31 were rejected under 35 USC §112, first paragraph, as failing to comply with the enablement requirement. The Examiner believes undue experimentation would be required to practice the invention of claims 30-31. The Examiner thus believes the Applicant has not shown how the method of the invention can be used to detect disorders.

In response, Applicant has amended claim 30 to call for the specific steps of contacting the proteons produced in a subsample with an antibody that binds to a protein, identifying the protein, and correlating the identified protein to a disorder. These latter disorders were originally defined in claim 31 and have now been incorporated into claim 30 which necessitated the cancellation of claim 31. Thus, claim 30 now specifies all of the steps necessary to show how the method of the invention can be used to detect disorders. As stated in Applicant's description, it is well known by those skilled in the art that certain proteins correlate to certain disorders. In view of this knowledge, once the protein bound in the subsample is identified, one can readily correlate the identified protein to a particular disorder, or at least eliminate particular disorders. For example, Applicant submits herewith four of the articles referred to in the description at the top of page 7. These articles clearly evidence the fact that it is well known in the art that the identification of various proteons is indicative of a disorder or disease state. Thus, Applicant believes it is not necessary to provide extensive examples on how the identification of various proteins correlate to the detection of various disorders. These

steps are well known to those skilled in the art. Thus, Applicant believes the Examiner should withdraw the §112 rejection based on enablement.

On page 12 of the Office Action, the Examiner objected to claims 21-32 under 35 USC §112, second paragraph, as being indefinite. With regard to claims 21-29, the Examiner indicated that claim 21, although claiming a method of cyclic amplification of proteons, did not have an end point specified. Accordingly, Applicant has rewritten claim 21 to call for heating the subsample, then determining the number of proteons in the sample, and finally, repeating the first three steps until the number of proteons determined to be in each heated subsample no longer increases. Applicant believes this adequately provides an end point to the method of claim 21. Also, the amendments to claim 21 are not new matter as they are clearly set forth in the description as filed.

At the top of page 13 of the Office Action, the Examiner objected to claims 22-29 under 35 USC §112, second paragraph, as once again not providing a clear end point. In response, Applicant notes that in view of the amendment to claim 21, claim 22 has been revised to merely state the additional step of correlating the number of proteons in the subsample to the number of misfolded proteins present in the sample. This step of correlation is predictive of the progress of a disease. Support can be found in the specification as filed at page 6, lines 17-26.

Also at the top of page 14 of the Office Action, claims 30-31 were rejected under 35 USC §112, second paragraph, as being indefinite for failing to provide a clear end point to the method. In response, as noted previously herein, claim 30 has been amended to add the steps of identifying the protein, and correlating the identified protein to a disorder. As a result, Applicant believes claim 30 now has a definite end point and adequately describes how the method for the detection of a disorder is accomplished. Thus, Applicant believes the Examiner should withdraw the objection to original claims 30-31.

Finally, Applicant notes that although original claim 20 has been rejected by the Examiner, there is no specific discussion of claim 20 anywhere in the Office Action. In

the previous Office Action dated August 10, 2004, claim 20 was "objected to," but once again, was not specifically discussed in the Office Action. Applicant believes claim 20 is distinguishable over the prior art as none of the prior art discusses or teaches the clearing of misfolded proteins from blood. The Examiner should note that Applicant has attempted to revise claim 20 so that it is definite and provides a clear end point. This was merely an attempt to avoid an anticipated §112, second paragraph, rejection. However, claim 20 now clearly states that a blood sample is contacted with a protein nucleation center for a period of time, and thereafter, the misfolded proteins are removed from the sample. Applicant believes claim 20 is now allowable, and respectfully requests the same herein.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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Opinion

Atherosclerosis: another protein misfolding disease?

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Abstract

The secondary structure and conformation of apo-B 100 in low-density lipoproteins (LDL) are imposed by lipid–protein interactions and dynamics, and affected by the introduction or removal of lipids during the course of lipoprotein metabolism. Following an alteration of the water–lipid interface as a result of, for example, oxidation of lipids, the supramolecular structure becomes destabilized and apoB can misfold. These events have been observed in LDL^-, a fraction of oxidatively modified LDL isolated *in vivo*. This modified lipoprotein possesses several atherogenic properties and represents an *in vivo* counterpart of *in vitro* modified LDL that is implicated in atherosclerosis. The misfolding of apoB, its aggregation, resistance to proteolysis, and cytotoxicity are common motifs shared by LDL^- and amyloidogenic proteins. Based on these analogies, we propose that atherogenesis could be considered as a disease produced by the accumulation of cytotoxic and pro-inflammatory misfolded lipoproteins.

Abstract

It is proposed that atherogenesis might be considered as a disease caused by the accumulation of cytotoxic and pro-inflammatory misfolded lipoproteins.

Author Keywords: atherosclerosis; protein misfolding; apoB; lipid oxidation; low-density lipoprotein

Subject-index terms: Molecular Medicine; Structural Biology

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Minireview

Protein misfolding and disease; protein refolding and therapy

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Abstract

Diverse human disorders, including several neurodegenerative diseases and systemic amyloidosis, are thought to arise from the misfolding and aggregation of an underlying protein. Recent findings strongly support this hypothesis and have increased our understanding of the molecular mechanism of protein conformational disorders. Many questions are still pending, but the data overall suggest that correction of protein misfolding constitutes a viable therapeutic strategy for conformational diseases.

Author Keywords: Protein conformational disorders; Amyloid; Protein misfolding; Therapy; β-Sheet breaker peptides

Article Outline

1. Introduction

The biological function of a protein depends on its tridimensional structure, which is determined by its amino acid sequence during the process of protein folding. In the last few years, diverse diseases have been shown to arise from protein misfolding and are now grouped together under the name of protein conformational disorders (PCDs) [1, 2, 3, 4 and 5]. This group includes Alzheimer's disease (AD), transmissible spongiform encephalopathies (TSEs), serpin-deficiency disorders, haemolytic anemia, Huntington disease (HD), cystic fibrosis, diabetes type II, amyotrophic lateral sclerosis (ALS), Parkinson disease (PD), dialysis-related amyloidosis and more than 15 other less well-known diseases (Table 1).

Table 1. List of some diseases that have been classified in the group of PCDs [2, 3, 4 and 5]

Protein involved	Diseases
Amyloid-β	AD
α-Synuclein	PD
Amylin	Diabetes type 2
SOD	ALS
β2-Microglobulin	Haemodialysis-related amyloidosis
Amyloid-A	Reactive amyloidosis
CFTR protein	Cystic fibrosis
Hemoglobin	Sickle cell anemia
Huntingtin	HD
PrP	Creutzfeldt–Jakob disease and related disorders
Ten other proteins	Systemic and cerebral heriditary amyloidosis

The hallmark event in PCD is a change in the secondary and/or tertiary structure of a normal protein without alteration of the primary structure. The conformational change may promote the disease by either gain of a toxic activity or by the lack of biological function of the natively folded protein [3 and 5] (Fig. 1). There is no evident sequence or structural homology among the proteins implicated in PCD. However, the striking feature of these proteins is their inherent ability to adopt at least two different stable conformations [5]. In most of PCDs the misfolded protein is rich in β-sheet conformation [4 and 5]. β-Sheets are one of the prevalent, repetitive secondary structures in folded proteins and are formed of alternating peptide pleated strands linked by hydrogen bonding between the NH and CO groups of the peptide bond. While in α-helices the hydrogen bonds are between groups within the same strand, in β-sheets the bonds are between one strand and another. Since the second β-strand can come from a different region of the same protein or from a different

molecule, formation of β-sheets is usually stabilized by protein oligomerization or aggregation. Indeed, in most PCDs the misfolded protein self-associates and becomes deposited in amyloid-like aggregates in diverse organs, inducing tissue damage and organ dysfunction [2] (Fig. 1).

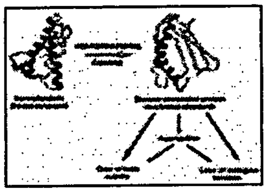

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Fig. 1. Protein misfolding and disease. A conformational change in a normal protein seems to be the hallmark event in a group of diverse diseases. Protein misfolding may be associated to disease by either the absence of biological activity of the folded protein or by a gain of toxic activity by the misfolded protein. Aggregation of the misfolded protein may also contribute to the disease pathogenesis.

2. Role of protein misfolding and aggregation in disease

Neuropathologic and genetic studies as well as the development of transgenic animal models have provided strong evidences for the involvement of protein misfolding in disease. Almost 100 years ago, the neuropathologist Alois Alzheimer described for the first time the typical aggregates in the brain parenchyma of demented people [6]. We now know that these aggregates, called amyloid plaques, are composed of protein fibrils. With the exception of cystic fibrosis and some forms of TSE, the end point of protein misfolding in PCD is aberrant protein aggregation and accumulation as amyloid-like deposits in diverse organs [2, 3, 7, 8 and 9]. The correlation and co-localization of protein aggregates with degenerating tissue and disease symptoms is a strong indication of the involvement of amyloid deposition in the pathogenesis of PCD [7, 8 and 9]. Moreover, protein deposits have become a typical signature of PCD and their presence is used for definitive diagnosis [10 and 11]. However, it is still a matter of controversy whether the deposits of aggregated protein are the culprit of the disease or an inseparable epiphenomenon [5, 12, 13 and 14].

Another important piece of evidence for the role of protein misfolding in disease comes from genetic studies [2, 15, 16, 17, 18 and 19]. Most PCDs have both an inherited and sporadic origin. Interestingly, mutations in the genes encoding the protein component of fibrillar aggregates are genetically associated with inherited forms of the disease. The familial forms usually have an earlier onset and higher severity than sporadic cases. In the familial cases, a mutation may destabilize the normal protein folding, favoring the misfolding and aggregation of the protein. Mutations in the respective fibrillar proteins have been associated with familial forms of many diseases, including AD, TSE, HD and related polyglutamine disorders, PD, amyloid polyneuropathy, cardiac amyloidosis, visceral amyloidosis, cerebral hemorrhage with amyloidosis of the Dutch and Icelandic type, cerebral amyloidosis of the British and Dannish type, thromboembolic disease, angioedema, emphysema, sickle cell anemia and ALS [2, 15, 16, 17 and 18].

Studies with transgenic animal models have been useful in understanding the contribution of

the misfolded protein in disease pathogenesis [19, 20, 21, 22, 23, 24 and 25]. Several pathological features of diverse PCDs have been induced in animals by incorporation of the human mutated gene for the protein undergoing misfolding. Transgenic mice that overexpress high levels of human amyloid precursor protein containing diverse mutations progressively develop many of the pathological hallmarks of AD, including cerebral amyloid deposits, neuritic dystrophy, astrogliosis, neuronal loss and cognitive and behavioral alterations [19, 23, 26 and 27]. ALS pathology has been produced in mice by overexpressing the human mutated superoxide dismutase (SOD) gene [19 and 28]. Some of these mice develop motor neuron dysfunction similar to ALS patients, and typical pathological alterations, including the presence of hyaline inclusion bodies in degenerating axons, muscle atrophy and wasting, astrocytes damage and extensive loss of large myelinated axons of motor neuronal cells. Recently, it was reported that transgenic mice expressing the wild-type human α-synuclein gene developed several of the clinico-pathological features of PD, including accumulation of Lewy bodies in neurons of the neocortex, hippocampus and substantia nigra, loss of dopaminergic terminals in the basal ganglia and associated motor impairments [29]. Transgenic mice containing the exon 1 of the human huntingtin and carrying 115–156 CAG repeat expansions develop pronounced neuronal intranuclear inclusions, containing the proteins huntingtin and ubiquitin, prior to developing a neurological phenotype [30]. The cerebral abnormalities were strikingly similar to those observed in HD patients. In addition, these mice develop a progressive neurological dysfunction with a movement disorder and weight loss similar to HD [31]. One of the first transgenic models showing a neurodegenerative process similar to a human disease was made by overexpression of the human mutated prion protein (PrP) gene [25 and 32]. Spontaneous neurologic disease with spongiform degeneration developed and these abnormalities have been transmitted to non-transgenic mice by inoculation of the sick brain homogenate. Finally, a transgenic mouse model with high rates of expression of human islet amyloid polypeptide (IAPP) spontaneously developed diabetes mellitus by 8 weeks of age, which was associated with selective β-cell death and impaired insulin secretion [24]. Small intra- and extracellular IAPP aggregates were present in islets of transgenic mice during the development of diabetes mellitus.

The generation of animal models showing clinical and pathological features similar to the disease by expressing the human protein involved in abnormal folding and aggregation strongly supports a critical role for protein misfolding and polymerization in the disease. However, temporal studies of the appearance of disease-like features in some of the transgenic models have shown that significant tissue damage and clinical symptoms appear before detection of protein aggregates [24, 26 and 33]. These findings suggest that a misfolded soluble intermediate, not yet deposited in the tissue, could be the real culprit of the PCD pathogenesis [5, 12, 13 and 14]. In this scenario, the formation of large protein aggregates deposited in the tissue could even be considered a protective event that allows the deposition and isolation of the toxic abnormally folded proteins.

3. Protein misfolding and aggregation: which comes first?

Protein misfolding is dependent upon conformational changes, which could be induced, stabilized or independent of protein oligomerization. The starting point in PCD is the natural protein folded in the native and active conformation which is usually a mixture of α-helical and random structure, and the end point is the same protein aggregated and adopting a β-pleated sheet conformation. It is unclear at present whether the misfolding triggers protein aggregation or rather protein oligomerization induces the conformational changes (Fig. 2).

The latter is not a purely academic debate, but it is very relevant for the design of effective therapeutic strategies.

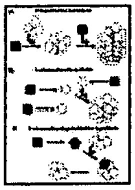

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Fig. 2. Models for the molecular mechanism of protein misfolding and aggregation. Three different hypotheses have been proposed to describe the relationship between conformational changes and aggregation. In the polymerization hypothesis (A), aggregation induces the protein conformational changes, while in the conformational hypothesis (B), protein misfolding is independent of aggregation, which is a non-necessary end point of conformational changes. The conformation/oligomerization model (C) represents an intermediate view in which slight conformational changes trigger oligomerization that is essential for the stabilization of protein misfolding. Square represents the folded native conformation, circles the disease-associated conformer and pentagon corresponds to an unstable conformational intermediate.

Based on kinetic modeling of protein aggregation, it has been proposed that the critical event in PCD is the formation of protein oligomers that act as seeds to induce protein misfolding [34, 35 and 36] (Fig. 2A). In this model, misfolding occurs as a consequence of protein aggregation (polymerization hypothesis), which follows a crystallization-like process dependent upon nucleus formation [34 and 35]. A nucleation-dependent polymerization process is characterized by a slow lag phase in which a series of unfavorable interactions occur to form an oligomeric nucleus that rapidly grows to form larger polymers [35] (Fig. 2A). The lag phase can be minimized or removed by addition of pre-formed nucleus or seeds. This hypothesis has a precedent in normal protein polymerization processes, such as microtubule formation.

The alternative model is that the underlying protein is stable in both the folded and misfolded forms in solution [3, 37, 38, 39 and 40] (conformational hypothesis). This hypothesis proposes that spontaneous or induced conformational changes result in the formation of the misfolded protein that may or may not aggregate (Fig. 2B). In this model, the formation of amyloid is a non-necessary end point of the conformational change, which can be an accompanying consequence rather than a direct cause of the disease [5, 37 and 40]. A central issue in the conformational hypothesis is the identification of the factors inducing the protein structural changes. Over the last few years, several factors have been described to play such a role [40 and 41], including mutations that destabilize the folded structure, modification on the environmental conditions (pH, oxidative stress, metal ions) and the activity of certain proteins collectively named pathological chaperones (apolipoprotein E, amyloid P component, protein X).

An intermediate view (Fig. 2C) is that slight conformational changes result in the formation of an amyloidogenic intermediate, which is unstable in an aqueous environment because of exposure of hydrophobic segments to the solvent (conformation/oligomerization hypothesis) [2, 5, 42 and 43]. This unstable intermediate is stabilized by intermolecular interactions with other molecules forming small β-sheet oligomers, which by further growth produce amyloid

fibrils [2, 42 and 43]. In this model the conversion of the folded protein into the pathological form is triggered by structural changes, but complete misfolding is dependent upon oligomerization. The presence of some degree of conformational changes prior to the formation of aggregates has been demonstrated for diverse proteins including transthyretin, serpins, amyloid-β and PrP [2, 4, 5 and 42].

The three models explain in variable degree most of the experimental results. However, it appears that the conformation/oligomerization hypothesis is the most comprehensive and accepted model of protein misfolding and aggregation.

4. Correcting protein misfolding as a novel therapeutic approach

Considering that protein misfolding and aggregation are central in the pathogenesis of PCD, a therapy directed to the cause of the disease should aim to inhibit and/or reverse the conformational changes that result in the formation of the pathological protein conformer.

Assuming that protein misfolding is triggered by conformational changes stabilized by protein oligomerization, an interesting strategy would be to preclude the stabilization of the misfolding or better to destabilize the monomeric intermediate and the early β-sheet oligomers. We have postulated that short synthetic peptides containing the self-recognition motif of the protein and engineered to destabilize the abnormal conformation might be useful to correct protein misfolding [4, 12 and 43]. These peptides called synthetic mini-chaperones are designed to be similar to the sequence of the protein region responsible for self-association and contain residues that specifically favor or disfavor a particular structural motif [4 and 43]. Considering that in most PDCs the misfolded protein is rich in β-sheet structure, we have focused mainly on the design of peptides to prevent and to reverse β-sheet formation (β-sheet breaker peptides) [43].

β-Sheet breaker peptides have, so far, been designed for blocking the conformational changes and aggregation undergone by both Aβ and PrP [4, 43, 44 and 45]. We have reported that 11- and 5-residue β-sheet breaker peptides, homologous to the central hydrophobic region of Aβ, inhibited and dissolved amyloid aggregates in vitro and in animal models of AD [44 and 46]. Furthermore, the 5-amino acid peptide prevented neuronal damage induced by amyloid both in cell culture and in a disease animal model [44 and 46]. Based on the same concept and using the PrP sequence 114–122 as a template, we have also produced β-sheet breaker peptides for the treatment of TSE [45]. Several in vitro, cell culture and in vivo assays were used to test the activity of the peptides and the results clearly indicate that it is possible not only to prevent the $PrP^{C} \rightarrow PrP^{SC}$ conversion, but more interestingly to reverse the infectious PrP^{SC} conformer to a biochemical and structural state similar to PrP^{C} [45].

These results together support the notion that synthetic β-sheet breaker peptides might be useful in destabilizing the β-sheet rich abnormal conformation, inducing its conversion into the normal form. Synthetic mini-chaperone peptides do not need to be restricted to breaking β-sheets [4 and 43]. Peptides can also be engineered to act as β-sheet promoters, α-helical breakers, β-turn promoters or even to induce a desired conformation in unstructured protein fragments. The principles to manipulate protein conformation may provide a general

platform technology to design drugs for the treatment of PDC. Moreover, our findings suggesting that protein conformation can indeed be specifically altered open a new approach for modifying phenotypic characteristics by modulating experimentally the structure of a selected protein. Therefore, the discovery of the principles for generating synthetic mini-chaperones could be useful as a novel therapeutic approach for disorders where the function of a protein needs to be modified.

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References

1. R.W. Carrell and D.A. Lomas. *Lancet* **350** (1997), pp. 134–138. Abstract | **Full Text + Links** | PDF (97 K)

2. J.W. Kelly. *Curr. Opin. Struct. Biol.* **6** (1996), pp. 11–17. Abstract | **Abstract + References** | PDF (738 K)

3. P.J. Thomas, B.-H. Qu and P.L. Pedersen. *Trends Biochem. Sci.* **20** (1995), pp. 456–459. Abstract | **Full Text + Links** | PDF (1182 K)

4. C. Soto. *J. Mol. Med.* **77** (1999), pp. 412–418.

5. R.W. Carrell and B. Gooptu. *Curr. Opin. Struct. Biol.* **8** (1998), pp. 799–809. Abstract | **Abstract + References** | PDF (1354 K)

6. A. Alzheimer. *Allg. Z. Psych. Gerichtl. Med.* **64** (1907), pp. 146–148.

7. W.G. Johnson. *J. Anat.* **196** (2000), pp. 609–616.

8. G.G. Glenner. *N. Engl. J. Med.* **302** (1980), pp. 1283–1292.

9. J.D. Sipe. *Ann. Rev. Biochem.* **61** (1992), pp. 947–975.

10. J.D. Gillmore, P.N. Hawkins and M.B. Pepys. *Br. J. Haematol.* **99** (1997), pp. 245–256.

11. P. Westermark. *Scand. J. Rheumatol.* **24** (1995), pp. 327–329.

12. P.B. Tran and R.J. Miller. *Trends Neurosci.* **22** (1999), pp. 194–197. Abstract | **Full Text + Links** | PDF (105 K)

13. C. Soto, G.P. Saborio and B. Permanne. *Acta Neurol. Scand.* **176** (2000), pp. 90–95.

14. M.S. Goldberg and P.T. Lansbury, Jr.. *Nat. Cell Biol.* **2** (2000), pp. E115–E119.

15. D.R. Jacobson and J.N. Buxbaum. *Adv. Hum. Genet.* **20** (1991), pp. 69–123.

16. J.N. Buxbaum and C.E. Tagoe. *Annu. Rev. Med.* **51** (2000), pp. 543–569.

17. S.B. Prusiner and M.R. Scott. *Annu. Rev. Genet.* **286** (1997), pp. 593–606.

18. D.J. Selkoe. *J. Biol. Chem.* **271** (1996), pp. 18295–18298.

19. D.L. Price, S.S. Sisodia and D.R. Borchelt. *Science* **282** (1998), pp. 1079–1083.

20. M.E. Gurney. *Bioessays* **22** (2000), pp. 297–304.

21. D.L. Price, P.C. Wong, A.L. Markowska, M.K. Lee, G. Thinakaren, D.W. Cleveland, S.S. Sisodia and D.R. Borchelt. *Ann. N.Y. Acad. Sci.* **920** (2000), pp. 179–191.

22. S. Araki, S. Yi, T. Murakami, S. Watanabe, S. Ikegawa, K. Takahashi and K. Yamarnura. *Mol. Neurobiol.* **8** (1994), pp. 15–23.

23. G. Emilien, J.M. Maloteaux, K. Beyreuther and C.L. Masters. *Arch. Neurol.* **57** (2000), pp. 176–181.

24. J. Janson, W.C. Soeller, P.C. Roche, R.T. Nelson, A.J. Torchia, D.K. Kreutter and P.C. Butler. *Proc. Natl. Acad. Sci. USA* **93** (1996), pp. 7283–7288.

25. C. Weissmann, M. Fischer, A. Raeber, H. Bueler, A. Sailer, D. Shmerling, T. Rulicke, S. Brandner and A. Aguzzi. *Rev. Sci. Tech.* **17** (1998), pp. 278–290.

26. F. Van Leuven. *Prog. Neurobiol.* **61** (2000), pp. 305–312. Abstract | **Full Text + Links** | PDF (117 K)

27. K. Duff. *Curr. Opin. Biotechnol.* **9** (1998), pp. 561–564. Abstract | **Abstract + References** | PDF (560 K)

28. D.L. Price, P.C. Wong, D.R. Borchelt, C.A. Pardo, G. Thinakaran, A.P. Doan, M.K. Lee, L.J. Martin and S.S. Sisodia. *Rev. Neurol. (Paris)* **153** (1997), pp. 484–495.

29. E. Masliah, E. Rockenstein, I. Veinbergs, M. Mallory, M. Hashimoto, A. Takeda, Y. Sagara, A. Sisk and L. Mucke. *Science* **287** (2000), pp. 1265–1269.

30. S.W. Davies, M. Turmaine, B.A. Cozens, M. DiFiglia, A.H. Sharp, C.A. Ross, E. Scherzinger, E.E. Wanker, L. Mangiarini and G.P. Bates. *Cell* **90** (1997), pp. 537–548.

31. K. Sathasivam, C. Hobbs, L. Mangiarini, A. Mahal, M. Turmaine, P. Doherty, S.W. Davies and G.P. Bates. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **354** (1999), pp. 963–969.

32. K.K. Hsiao, M. Scott, D. Foster, D.F. Groth, S.J. DeArmond and S.B. Prusiner. *Science* **250** (1990), pp. 1587–1590.

33. D. Moechars, I. Dewachter, K. Lorent, D. Reverse, V. Baekelandt, A. Naidu, I. Tesseur, K. Spittaels, C.V. Haute, F. Checler, E. Godaux, B. Cordell and F. Van Leuven. *J. Biol.*

Chem. **274** (1999), pp. 6483–6492.

34. J.T. Jarrett and P.T. Lansbury, Jr.. *Cell* **73** (1993), pp. 1055–1058. Abstract | **Full Text + Links** | PDF (523 K)

35. J.D. Harper and P.T. Lansbury, Jr.. *Annu. Rev. Biochem.* **66** (1997), pp. 385–407.

36. A. Lomakin, D.B. Teplow, D.A. Kirschner and G.B. Benedek. *Proc. Natl. Acad. Sci. USA* **94** (1997), pp. 7942–7947.

37. F.E. Cohen and S.B. Prusiner. *Ann. Rev. Biochem.* **67** (1998), pp. 793–819.

38. D.R. Booth, M. Sunde, V. Bellotti, C.V. Robinson, W.L. Hutchinson, P.E. Fraser, P.N. Hawkins, C.M. Dobson, S.E. Radford, C.C.F. Blake and M.B. Pepys. *Nature* **385** (1997), pp. 787–793.

39. R.N. Sifers. *Nat. Struct. Biol.* **2** (1995), pp. 355–357.

40. S.B. Prusiner. *Proc. Natl. Acad. Sci. USA* **95** (1998), pp. 13363–13383.

41. C. Soto, J. Ghiso and B. Frangione. *Alzheimer's Res.* **3** (1997), pp. 215–222.

42. L.C. Serpell, M. Sunde, P.E. Fraser, P.K. Luther, E.P. Morris, O. Sangren, E. Lundgren and C.C.F. Blake. *J. Mol. Biol.* **254** (1995), pp. 113–118. Abstract | PDF (1555 K)

43. C. Soto. *CNS Drugs* **12** (1999), pp. 347–356.

44. C. Soto, E.M. Sigurdsson, L. Morelli, R.A. Kumar, E.M. Castano and B. Frangione. *Nat. Med.* **4** (1998), pp. 822–826.

45. C. Soto, R.J. Kascsak, G.P. Saborio, P. Aucouturier, T. Wisniewski, F. Prelli, R. Kascsak, E. Mendez, D.A. Harris, J. Ironside, F. Tagliavini, R.I. Carp and B. Frangione. *Lancet* **355** (2000), pp. 192–197. Abstract | **Full Text + Links** | PDF (312 K)

46. E.M. Sigurdsson, B. Permanne, C. Soto, T. Wisniewski and B. Frangione. *J. Neuropathol. Exp. Neurol.* **59** (2000), pp. 11–17.

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Conformational changes and disease — serpins, prions and Alzheimer's

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Abstract

Some of the most perplexing disorders in medicine are each now known to arise from the conformational instability of an underlying protein. The consequence is a continuum of pathologies with typically a change in fold leading to ordered aggregation and tissue deposition. The serpins provide a structural prototype for these pathologies and give a perspective on the assessment of current proposals as to the conformational basis of both Alzheimer's disease and the transmissible prion encephalopathies.

Abbreviations: **BSE** bovine spongiform encephalopathy; **nvCJD** new variant Creutzfeldt—Jakob disease; **PAI** plasminogen activator inhibitor; **PrP^{c}** prion protein (normal conformation); **PrP^{Sc}** prion protein (abnormal conformation); **T$_{m}$** protein melting (transition) temperature

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Review

Conformational disease

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Summary

Several diverse disorders, including the prevalent dementias and encephalopathies, are now believed to arise from the same general disease mechanism. In each, there is abnormal unfolding and then aggregation of an underlying protein. The gradual accumulation of these aggregates and the acceleration of their formation by stress explain the characteristic late or episodic onset of the clinical disease. The understanding of these processes at the molecular level is opening prospects of more rational approaches to investigation and therapy.

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